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International University of Health and Welfare (IUHW) Graduate School,
Japan

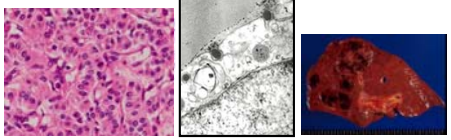
Neuroendocrine tumors

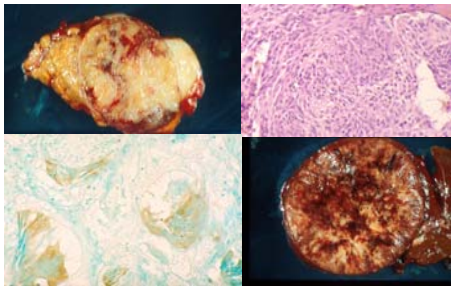
Learning Objectives:

1. What are the neuroendocrine tumors and where do they occur
Are they benign or malignant tumors?
2. New WHO classification of
Pancreatic neuroendocrine neoplasms(NEN) 2017

3. Cytological appearance of NETs

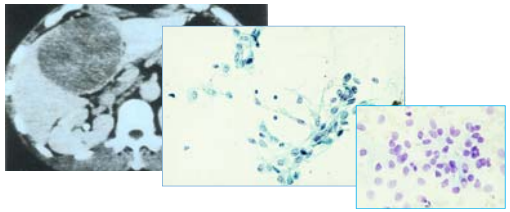
Neuroendocrine tumor(NET)
NEN NET NEC
Production and secretion of
peptide hormones and amines
1. Diagnostic morphology
2. Secretory granules: dense core
3. Neuroendocrine markers:SNP CGA CD56
4. Tumors with wide spectrum of malignancy





Pancreatic somatostatinoma Liver metastasis
Brain metastasies after 10 years

A 52 year old male was found to have hepatomegaly.
He was otherwise free of symptoms
FNA was performed.



Metastatic pancreatic endocrine tumor
was suggested by "a smart" cytopathologist

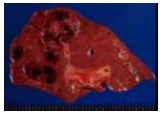
Somatostatinoma of the pancreas with metastases to the liver and the brain

Lessons we learn from this case:neuroendocrine tumor(NET)

1. A nodule in the liver can be NET, metastatic
2. FNA can play an important role for definite diagnosis
3. In many cases, when NETs are found they already metastasized
4. NETs are non-functioning in many cases clinically, but cellular levels they may produce hormones
5. Some cases follow worse prognosis, systemic metastases

NET Clnical Presentation

1. Symptoms are often absent or vague
   -Approximately 58-71% of pNET are non-functioning
2. More than half of NET are metastatic at diagnosis
3. 65% of patients with advanced NET will no longer be alive in 5 years



Simron Singh,MD Toronto Canada NETour Tokyo 9-17-11

New pathological classification

1. Definite(no carcinoid)
2. Prognostic
3. Predictive

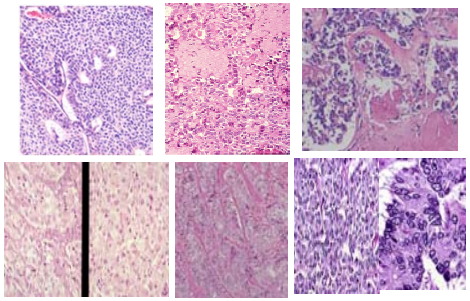
Neuroendocrine tumors include

Pituitary adenomas
Thyroid medullary carcinoma
Gastro-enteric NET *GEPNET
Pancreatic NET
Pheochromocytomas & paragangliomas
Pulmonary NET
NET of the skin
NET of other location

Neuroendocrine tumors include

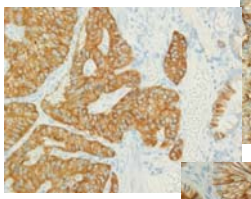
Pituitary adenomas
Thyroid medullary carcinoma
Gastro-enteric NET ***GEPNET**
Pancreatic NET
Pheochromocytomas & paragangliomas
Pulmonary NET
NET of the skin
NET of other location
***Frequent clinical problems, such as liver and lymph node metastases**

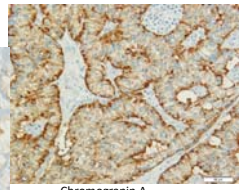
Recognition of neuroendocrine histology(pattern)



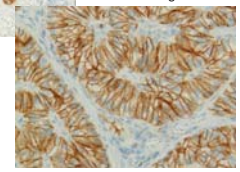
Various neuroendocrine tumors(H&E staining)
Pancreatic NET(ACTH producing) Pancreatic NET(insulinoma Medullary thyroid ca(MTC)
Pheochromocytoma Rctal WDNET(carcinoid) Hepatic WDNET(carcinoid)

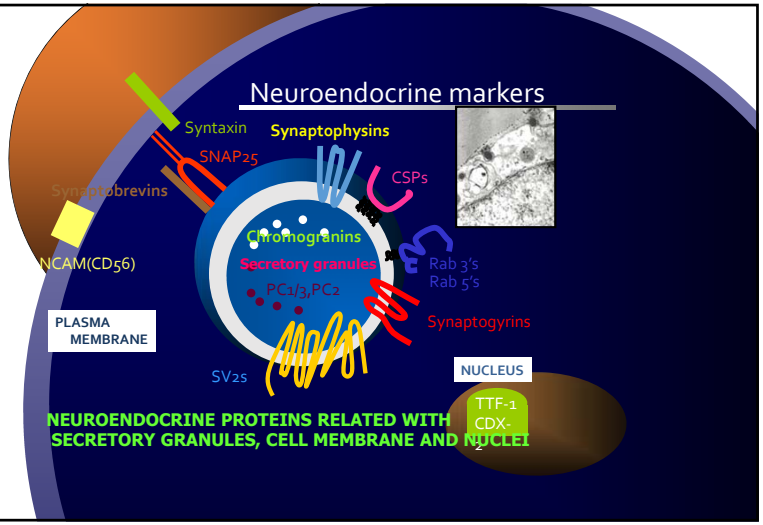
Neuroendocrine markers


Synaptophysin


Chromogranin A

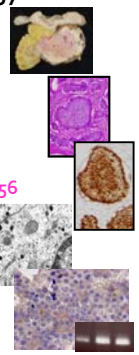
Duodenal neuroendocrine tumor


CD56

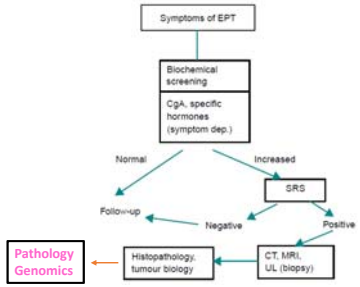


Diagnostic algorithm:Pathology

1. Gross examination
2. Microscopic examination
   "neuroendocrine" appearance
   *Roles of pathologists
3. Immunohistochemistry
   for "neuroendocrine markers"
   Synaptophysin chromogranin A CD56
4. Electron microscopy
   for (neuro)secretory granules
5. Molecular pathology
   Point mutation MEN1 VHL
6. Molecular targets for therapy
   SSTR2



Oberg K et al. Best Pract Res Clin Gastroenterol. 2005 19(5) 753-81



Diagnostic algorithm for endocrine pancreatic tumours (EPTs). CgA, chromogranin A; CT, computed tomography; MRI, magnetic resonance imaging

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WHO Classification 2017

Comparison of the WHO classifications of pancreatic neuroendocrine neoplasms

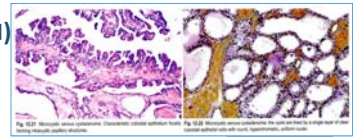
WHO 1980	WHO 2000/2004	WHO 2010	WHO 2017
Islet cell tumour (adenoma/ carcinoma)	Well-differentiated endocrine tumour/carcinoma (WDET; WDEC)	Neuroendocrine tumour NET G1/G2	Neuroendocrine tumour **NET G1/G2/G3** (Well differentiated neuroendocrine neoplasm)
Poorly differentiated endocrine carcinoma	Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC)	Neuroendocrine carcinoma NEC G3 large or small cell type	Neuroendocrine carcinoma **NEC G3** (Poorly differentiated neuroendocrine neoplasm), large or small cell type
	Mixed exocrine-endocrine carcinoma (MEEC)	Mixed adeno-neuroendocrine carcinoma (MANEC)	Mixed neuroendocrine-nonneuroendocrine neoplasm (**MiNEN**)
Pseudotumour lesions	Tumour-like lesions (TLL)	Hyperplastic and preneoplastic lesions	

WHO 2010	WHO 2017
Neuroendocrine tumour NET G1/G2	Neuroendocrine tumour **NET G1/G2/G3** (Well differentiated neuroendocrine neoplasm)
Neuroendocrine carcinoma NEC G3 large or small cell type	Neuroendocrine carcinoma **NEC G3** (Poorly differentiated neuroendocrine neoplasm), large or small cell type
Mixed adeno-neuroendocrine carcinoma (MANEC)	Mixed neuroendocrine-nonneuroendocrine neoplasm (**MiNEN**)
Hyperplastic and preneoplastic lesions	

Differetial diagnosis of PNET

Serous cystic neoplasm(SCN)

Clear cells
Low MW keratin MUC6 Inhibin
Sometimes SYN + NSE+

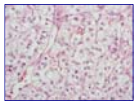


WHO 2010

Solid pseudopapillary neoplasm (SPN) * Next slide

VHL associated NET

Clear cell NET
CC RCC



Sporadic NET, MEN1 NET Sometimes Clear cytoplasm

Kasajima & Sasano 2014

Differential Diagnosis between PanNET and Adenocarcinoma(PDAC)

Jiao Y et al. Science. 2011 331(6021) 1199-203.
DAXX/ATRX, MEN1, and mTOR Pathway
Genes Are Frequently Altered in Pancreatic Neuroendocrine Tumors.

Table 1. Comparison of commonly mutated genes in PanNETs and PDAC based on 68 PanNETs and 114 PDACs.

Genes*	PanNET	PDAC†
* *MEN1*	44%	0%
DAXX, ATRX	43%	0%
* Genes in mTOR pathway	15%	0.80%
TP53	3%	85%
KRAS	0%	100%
CDKN2A	0%	25%
TGFBR1, SMAD3, SMAD4	0%	38%

With modification

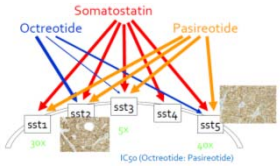
DAXX (death-domain–associated protein) and
ATRX (a thalassemia/mental retardation syndrome X-linked).

PanNET:Non-familial
Mutation:Somatic mutation from sections

Therapy of neuroendocrine tumors

Surgery
Chemotherapy

Molecular Targeted Therapy
Somatostatin analogues
Octreotide Pasireotide
mTOR inhibitor
Sunitinib



Biomarkers:Somatostatin receptors(SSTR2,5)
mTOR

Molecular targeted therapy for NET and NEC

SANDOSTATIN® LAR®
(octreotide acetate)
Treatment of patients with acromegaly:
Treatment of patients with symptoms associated with functional gastro-entero-pancreatic endocrine tumours Treatment of patients with advanced Neuroendocrine Tumours of the midgut or unknown primary tumour location.

Everolimus(Affinitor®)
adults with progressive neuroendocrine tumors of pancreatic origin (PNET)that are unresectable, locally advanced or metastatic.

SUTENT® is a kinase inhibitor indicated for the treatment of:
Progressive, well-differentiated pancreatic neuroendocrine tumors(pNET) in patients with unresectable locally advanced or metastatic disease.

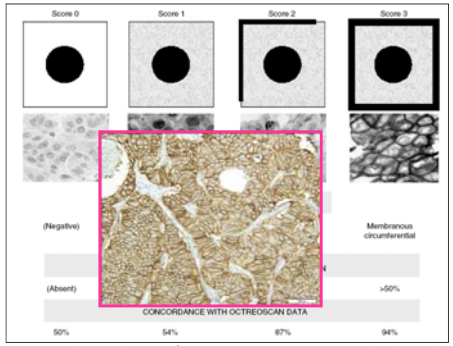


Figure3 Schematic illustration of somatostatin receptor type 2A immunohistochemical scoring system and its concordance rate with 111In-pentetreotide *in vivo* imaging.

Volante M *et al.* Modern Pathology 20:1172-82,2007

Genomics of neuroendocrine tumors

Hereditary tumors:germline mutation

Genetic syndromes associated with PanNETs

Syndrome	Affected gene	Prevalence in PanNETs (%)
Multiple endocrine neoplasia type 1	*MEN1*	20–70
Von Hippel–Lindau	*VHL*	≤20
Neuro bromatosis type 1	*NF1*	≤10
Tuberous sclerosis complex	*TSC2*	Rare (~1)

Abbreviation: PanNETs, pancreatic neuroendocrine tumors.

Nat Rev Gastroenterol Hepatol. ; 9(4): 199–208.

Well-differentiated pancreatic neuroendocrine tumors: from genetics to therapy

Roeland F. de Wilde, Barish H. Edil, Ralph H. Hruban, and **Anirban Maitra**
The Sol Goldman Pancreatic Cancer Research Center, Department of Pathology (R. F. de Wilde, R. H. Hruban, A. Maitra), Department of Surgery (B. H. Edil), The Johns Hopkins University School of Medicine, 1550 Orleans Street Baltimore, MD 21231, USA

Pancreastic endocrine tumors(PNET) can occur with familial background. They are autosomal dominant.

Hereditary neoplasms

Multiple Endocrine Neoplasia Type 1
von Hippel-Lindau Disease
Neurofibromatosis Type -1
Tuberous Sclerosis Complex

Genetic alteration is widely spread in the genes, menin and VHL.

In MEN1, PNET are most frequently gastrinoma and frequent multiple.
In VHL, PNET tend to be malignant.

Other familial background can give rise to the PNETs.

Genetic marker study is recommended for the appropriate diagnosis.

Endoscopic ultrasound-guided fine needle aspiration: EUS-FNA

Pancreatic tumors Diagnosis

Adenocarcinoma

Neuroendocrine tumors(NET)

Endocr Pathol (2014) 25:65–79
DOI 10.1007/s12022-013-9295-2

Neuroendocrine Tumors of the Pancreas: Current Concepts and Controversies

Michelle D. Reid · Serdar Balci · Burcu Saka · N. Volkan Adsay

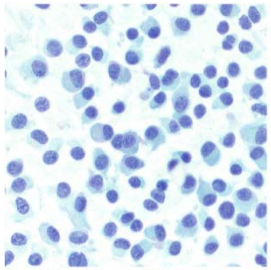


Fig. 10 Fine needle aspiration of a well-differentiated pancreatic neuroendocrine tumor showing singly dispersed, bland tumor cells with plasmacytoid morphology, oval nuclei, and "salt and pepper" chromatin (Papanicolaou stain, ×400 magnification)

Cytology of PNET
Plasmacytoid morphology
Salt and pepper nuclei

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References:

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Schott M., et al., Neuroendocrine neoplasms of the gastrointestinal tract. Dtsch Arztebl Int. 2011 May;108(18):305-12.

Heetfeld M., et al., Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer. 2015 Aug;22(4):657-64.

Basturk O., et al., The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. Am J Surg Pathol. 2015 May;39(5):683-90

Reid MD., et al., Neuroendocrine tumors of the pancreas: current concepts and controversies. Endocr Pathol. 2014 Mar;25(1):65-79

Volante M., et al., Somatostatin receptor type 2A immunohistochemistry in neuroendocrine tumors: a proposal of scoring system correlated with somatostatin receptor scintigraphy. Mod Pathol. 2007 Nov;20(11):1172-82.